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Lung Cancer Risk, Occupational Exposure, and the Debrisoquine Metabolic Phenotype[1]

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ABSTRACT

The risk of lung cancer in smokers was examined based on the debrisoquine metabolic phenotype and on exposure to occupational lung carcinogens, specifically asbestos and polycyclic aromatic hydrocarbons. Extensive metabolizers of debrisoquine are at a 4-fold increased risk for lung cancer compared to poor metabolizers, after adjustment for age, sex, and smoking (pack-years), when only occupationally unexposed subjects are considered. Increased risk related to the debrisoquine metabolic phenotype was greatest for squamous and small cell histologies, and least for the adenocarcinoma subtype. Men with a history of exposure to occupational carcinogens had significantly increased risk of lung cancer (relative risk = 2.8), after adjustment for age and smoking. Considering the combined effect of the high risk extensive metabolizers debrisoquine metabolic phenotype and likely occupational exposure to asbestos, the relative excess risk for lung cancer was 18-fold. This finding is consistent with a synergism in risk between the ability to extensively metabolize debrisoquine and occupational exposure to lung carcinogens in male smokers. Debrisoquine phenotyping has potential for identifying carcinogen-exposed workers at high risk of lung cancer.

INTRODUCTION

Ayesh and coworkers have reported that among smokers, the ability to metabolize debrisoquine by oxidation is associated with susceptibility to lung cancer (1). This observation has been confirmed in a subsequent study (2). Debrisoquine metabolism is genetically determined on the basis of family studies (3, 4), genetic linkage studies (5), and enzyme studies (6). Recently, human P450db1 (the specific human isozyme metabolizing debrisoquine) complementary DNA has been cloned and expressed in mammalian cell culture and the molecular defects of three different individual PMs[4] elucidated (7, 8). The risks based on this putative genetic risk factor both alone and in combination with exposure to known occupational lung carcinogens such as asbestos and PAHs have not been evaluated. In light of this we have undertaken a further analysis of the original British data. We extend their report of the association of lung cancer and the genetically determined ability to metabolize debrisoquine extensively and examine the implications of this risk factor for certain subgroups expected to be at high risk for lung cancer because of exposure to occupational lung carcinogens.

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[4] The abbreviations used are: PM, poor metabolizer; PAH, polycyclic aromatic hydrocarbons; EM, extensive metabolizer; IM, intermediate metabolizer; MP, metabolic phenotype; MR, metabolic ratio; RR, relative risk; CI, confidence interval.

MATERIALS AND METHODS

Patients for this study were identified at a chest outpatient clinic or as in-patients on two chest wards at the Whittington Hospital, London, over a 1-year period (1982 to 1983). This hospital receives referrals with chest problems in the catchment area of the Northwest Thames Regional Health Authority of London. The lung cancer patients (n = 245) had a definite diagnosis of bronchogenic carcinoma, excluding mesothelioma and other thoracic tumors, from samples obtained at bronchoscopy (194), transcutaneous needle biopsy (24), mediastinoscopy (nine), pleural biopsy (six), or multiple procedures (12). Control subjects (n = 234) had a confirmed diagnosis (including pulmonary function tests) of either asthma, bronchitis, or emphysema. All study subjects were caucasians of northern European origin and had a history of cigarette smoking. Subjects were excluded from study who had a history of other cancers, organ failure, incapacity or dementia, angina, or concomitant or previous chemo- or radiotherapy. Subjects who used drugs known or suspected to influence the metabolism of debrisoquine were also excluded. These drugs included those which inhibit debrisoquine metabolism competitively (phenformin) or noncompetitively (dextropropoxyphene); induce cytochrome P-450 enzymes (phenobarbital); or interfere with the debrisoquine assay (metformin and flucloxacillin). Other medication use was recorded.

For each study subject, a general nonstructured occupational history was taken. Questions were asked about temporary and principal jobs held. Specific questions regarding asbestos exposure were asked. Data available for analysis included the usual occupation and any history of asbestos exposure. The occupation data was reviewed without knowledge of case or debrisoquine metabolism status, and subjects were placed in one of three categories: unlikely, possible, or likely occupational exposure to PAHs, and asbestos. These categories were formed using the limited available information on job history. Individuals classified as having "likely" exposure to asbestos had worked in occupations such as pipe fitters, shipyard workers, boilermen, or in the construction trades; or had stated exposure to asbestos. Those with "likely" exposure to PAHs had worked for example as forklift operators, asphalt workers, or truck drivers. Subjects with no stated exposure who worked in settings considered unlikely to encounter occupational lung carcinogens, *e.g.*, housewives, office workers, were classified as "unlikely" with regard to each exposure. Individuals that fit neither category were classified as "possible" with regard to occupational exposure. Based on the available information, we identified no subjects with clear exposure to other lung carcinogens, *e.g.*, radon or arsenic.

Pack-years of cigarette consumption were calculated based on the usual cigarette use and the number of years of cigarette consumption.

Each patient received no drugs from 1130 p.m. the day before the test until 900 a.m. the day of the test. At 700 a.m. each study subject was given a 10-mg debrisoquine (Declinax, Roche) tablet orally; all urine was collected for the subsequent 8 h. The content of debrisoquine and 4-hydroxydebrisoquine in the urine was analyzed by electron capture gas chromatography. Individuals were phenotyped based on a calculated metabolic ratio,

$$\text{MR} = \text{debrisoquine/4-hydroxy-debrisoquine} \qquad \text{(A)}$$

based on an assay performed on an aliquot from the 8-h urine sample. Three metabolic phenotypes were defined; extensive (EM) (MR < 1),

Table 1 *Selected characteristics of lung cancer cases and chronic obstructive pulmonary disease controls*

	Lung cancer		COPD[a]	
	X^b	(SD)[c]	X	(SD)
Mean age	66.5	(7.4)	67.2	(6.6)
Pack-years	60.3	(23.9)	59.4	(21.1)
Sex (M:F)	159:86		153:81	
Mean urine (vol. 8 h)	666	(362)	741	(410)
	Percentage of metabolite recovery (SD)			
Debrisoquine	9.2	(8.3)	19.7	(18.0)
Hydroxydebrisoquine	16.5	(14.6)	10.8	(12.0)
Total	25.7	(19.1)	30.5	(23.5)

[a] COPD, chronic obstructive pulmonary disease controls.
[b] X, arithmetic mean.
[c] SD, standard deviation.

intermediate (IM) ($1 < MR < 12.6$), or poor (PM) ($MR > 12.6$) metabolizers. These are the definitions which have been used in previous work (1).

We used a maximum likelihood method to generate an alternate definition of the metabolic phenotypes. This method is described in detail elsewhere.[5] Briefly, the controls were assumed to be a mixture of three normal distributions, one for each phenotypic group (EM, IM, and PM). Cut points for the categorization of MR's into groups were determined by calculating curve crossing points for the adjacent distributions, corresponding to each phenotype. Using this method the phenotypes are defined as follows: EM ($MR < 1.93$), IM ($1.93 < MR < 20.8$), PM ($MR > 20.8$). Odds ratios are calculated using the new phenotype definitions derived using this method. Selected duplicate tables using the traditional breakpoints [EM ($MR < 1$), IM (1–12.6), PM ($MR > 12.6$)] are included. (see "Appendix" Tables 1 and 2).

For the statistical analysis, the odds ratio is used as an estimate of RR throughout. RR and confidence limits (CI 95%) adjusted for age, sex, pack-years of cigarette use, and occupational lung carcinogen exposure (unlikely, possible, likely) were determined by logistic regression (9, 10). For selected analyses, the excess risk and the relative excess risk due to interaction were calculated (11, 12).

RESULTS

The age, pack-years smoking, sex ratio, and urine volume, were similar in the cases and controls (Table 1). Although more 4-hydroxydebrisoquine is recovered in cases and more unchanged drug (debrisoquine) is recovered in controls, the sum of these two quantities is similar (Table 1). The age and sex distribution of the study group members by histological subtype is shown in Table 2.

For the analysis of lung cancer risk with respect to debrisoquine metabolism, individuals were classified based on the MP category, that is EM, IM, or PM (Table 3). In this analysis only subjects with no occupational exposure were included. Compared to the PM group, adjusted relative risk for lung cancer in the IM group does not differ significantly (RR = 0.6; 95% CI = 0.1–2.7). For the EM group however, there is a 4-fold increased risk of lung cancer RR = 4.3 (CI 95%, 1.1–16.3).

The data show little difference in risk between the PM and IM groups. Therefore in the remaining analyses, the PM and IM groups were combined to enhance the stability of the risk estimates. Again, in this analysis by lung histological subtype, individuals with occupational exposure are excluded. For each histological type the adjusted RR are somewhat higher for females than for males (Table 4). For both sexes, the lowest risk is associated with the adenocarcinomas. For this histological subtype, the relative risk is elevated but does not achieve statistical significance. Although the relative risks appear elevated in females for each histological type, there is wide overlap of the confidence intervals and the lower level of the confidence interval for females is similar to that for males, reflecting smaller numbers of women in the study.

The risk for lung cancer was assessed in relation to a job history of possible or likely exposure to lung carcinogens in Table 5. For this analysis only men were included, because only one woman was exposed. For men with possible exposure to asbestos the RR = 1.2 (CI 95%, 0.7–2.2). For men with likely exposure the RR = 2.9 (CI 95%, 1.1–7.7). Similarly, for men with possible and likely exposure to PAHs the associated risks were RR = 1.5 (CI 95%, 1.0–2.5) and RR = 2.4 (CI 95%, 0.8–7.4). These estimates are adjusted for age, the carcinogen not directly considered, and cigarette smoking (pack-years).

In Table 6, the risks associated with debrisoquine metabolic phenotype and occupational exposure to asbestos, and PAHs are shown. For each occupational exposure, the risk associated with no exposure among PM/IM of debrisoquine is considered the referent. There is a trend towards increased risk with exposure within each type of occupational lung carcinogen, but significantly increased risk only results in EM. Within the group of EM, the risk for lung cancer increases further with possible and with likely exposure to both occupational lung carcinogens. The risk among EM with likely PAH exposure is 35-fold (95% CI, 3.9–317) compared to nonexposed PM/IM. An 18-fold elevated risk is found for asbestos exposure (95% CI, 4.6–61.4).

As an estimate of interaction, the individual and joint effects of each occupational exposure and of the EM phenotype were determined in men. The method used for this analysis is from Rothman. RR_{occ} is the relative risk of occupational exposure, (either asbestos, PAH, or either) in the absence of the high risk debrisoquine phenotype (*i.e.*, EM). RR_{em} is the relative risk in individuals with the high risk metabolic phenotype (EM) with no occupational exposure. $RR_{em/occ}$ is the relative risk in individuals with both occupational exposure and the high risk debrisoquine metabolic phenotype. The relative excess risk due to interaction (RERI) is then calculated by the following formula:

$$RERI = RR_{em/occ} - RR_{em} - RR_{occ} + 1 \qquad (B)$$

An example of the calculation is given for asbestos. The excess risk associated with likely asbestos exposure ($RR_{occ\text{-}1}$) is 0.8; the excess risk associated with EM status ($RR_{em\text{-}1}$) is 5.0; and, the relative excess risk due to interaction ($RR_{em/occ} - RR_{occ} - RR_{em} + 1$) is 11.6. Results of similar calculations for PAH are shown in Table 7. This calculation assumes an additive model, however a calculation using a multiplicative model yields a similar result (calculations not shown) (13). These results are consistent with interaction between occupational carcinogen exposure and the extensive debrisoquine MP in male smokers.

When nonoccupationally exposed PM are considered as the referent for assessment of the risk among EMs, the calculated risk estimates among those with unlikely, possible, and likely exposure to occupational lung carcinogens are similar to those shown in Table 6 in which the referent includes PM and IM.

Appendix Tables 1 and 2 present the same calculations shown in Tables 4 and 6 except that the old cutpoints previously used to define the debrisoquine metabolic phenotypes are used. The risk of debrisoquine EMs by lung tumor histology and occupational exposure are comparable.

[5] N. Caporaso, L. Pickle, S. Bale, R. Ayesh, M. Hetzel, and J. Idle. The distribution of debrisoquine metabolic phenotypes and implications for the hypothesized association with lung cancer, in press, Genetic Epidemiology, 1989.

Table 2 *Distribution of study group by age, sex, and histological subtype*

	Male (age)					Female (age)				
	30–59	60–64	65–69	70+	Total	30–59	60–64	65–69	70+	Total
Lung cancer	25	17	55	62	159	26	27	25	18	86
Squamous cell	7	4	42	38	91	10	13	15	7	45
Small cell	14	6	9	9	38	14	3	8	5	30
Adenocarcinoma	4	5	3	10	22	1	1	2	4	8
Large cell	0	2	0	3	5	1	0	0	2	3
Other and unspecified	0	0	1	2	3	0	0	0	0	0
COPD[a] controls	18	34	55	46	153	7	20	27	27	81

[a] COPD, chronic obstructive pulmonary disease.

DISCUSSION

The present study demonstrates that the genetically determined ability to metabolize debrisoquine efficiently is associated with a marked excess risk for lung cancer among smokers who are occupationally exposed to lung carcinogens. The data suggest that the risk for occupationally related lung cancer is relatively low among PM/IM, although small numbers of exposed subjects in this group make the estimates of risk uncertain. The results cannot be attributed to differences between the study groups with regard to age or cigarette use. Due to the lack of women with likely exposure to occupational lung carcinogens, we could not adequately assess the effect of sex on this association. The entire study group had a history of cigarette smoking, so conclusions cannot be generalized to nonsmokers.

The genetics of debrisoquine metabolism in human populations has been well described. The PM phenotype is a Mendelian autosomal recessive trait. The EM phenotype is dominant and the degree of dominance has been estimated at 30% (3, 14). Population studies indicate that determining the MP based on the metabolic ratio, *i.e.*, PM (>12.6), IM (1–12.6), and EM (<1) is a reasonable reflection of the distribution of genotypes in the population. Using the maximum likelihood method referred to earlier, with the resulting new MP definitions, there is a higher probability that the phenotype reflects the true genotype. However, for a given individual the MP may not always precisely reflect genotype. More specifically, while in-

Table 3 *Relative risk by the debrisoquine metabolic phenotype in subjects with no occupational exposure*

	Debrisoquine metabolic phenotype		
	PM	IM	EM
MR[a]	(>20.8)	(1.9–20.8)	(<1.9)
Study group			
Lung cancer	3	11	116
COPD[b]	9	52	81
RR[c]	1.0	0.6	4.3
(95% CI)		(0.1–2.7)	(1.1–16.3)

[a] MR, metabolic ratio, used to classify individuals into metabolic phenotype categories.
[b] COPD, chronic obstructive pulmonary disease.
[c] RR, the relative risk is adjusted for age (30–59, 60–64, 65–69, 70+), sex, pack-years smoking (<40, 41–50, 51–70, 71+).

Table 4 *Relative risk of lung cancer among debrisoquine EM compared to combined PM/IM by gender and histological sub-type in individuals with no occupational exposure*

	Males	Females	Total
Cell type	RR (95% CI)	RR (95% CI)	RR (95% CI)
Squamous cell	4.1 (1.2–13.6)	14.5 (3.2–65.8)	7.9 (3.2–19.6)
Small cell	7.9 (0.9–67.8)	18.1 (2.3–143.7)	12.7 (2.9–55.6)
Adenocarcinoma	0.8 (0.2–2.9)	4.3 (0.4–47.1)	1.5 (0.5–4.6)
All histologies	3.1 (1.4–7.2)	13.7 (4.5–42.2)	6.2 (3.3–11.9)

Table 5 *Relative risk[a] of lung cancer in males by occupational exposure to lung carcinogens*

	Occupational exposure		
	Case	CTL	RR (95% CI)
Asbestos[b]			
None	111	121	1.0
Possible	31	26	1.2 (0.7–2.2)
Likely	17	6	2.9 (1.1–7.7)
PAH[c]			
None	76	91	1.0
Possible	72	57	1.5 (1.0–2.5)
Likely	11	5	2.4 (0.8–7.4)

[a] Adjusted for age and smoking (pack-years).
[b] Also adjusted for PAH (none, possible, likely).
[c] Also adjusted for asbestos (none, possible, likely).

Table 6 *Relative risk[a] of lung cancer in males by occupational exposure to lung carcinogens and by debrisoquine MP occupational exposure*

	Debrisoquine MP					
	PM/IM			EM		
	Case	CTL	RR (95% CI)	Case	CTL	RR (95% CI)
Asbestos[b]						
None	14	53	1.0	97	68	6.0 (3.0–12.0)
Possible	2	12	0.6 (0.1–3.0)	29	14	8.0 (3.3–19.6)
Likely	1	3	1.8 (0.2–19.6)	16	3	18.4 (4.6–74)
PAH[c]						
None	12	38	1.0	64	53	3.9 (1.8–8.4)
Possible	4	26	0.4 (0.1–1.8)	68	31	7.8 (3.5–17.4)
Likely	1	4	0.7 (0.1–6.7)	10	1	35.3 (3.9–317)

[a] Adjusted for age and smoking (pack-years).
[b] Also adjusted for PAH exposure (unlikely, possible, probable).
[c] Also adjusted for asbestos exposure (unlikely, possible, probable).

Table 7 *Excess relative risk due to interaction of occupational lung carcinogen exposure and the extensive metabolizer debrisoquine metabolic phenotype*

	Asbestos	PAH
PR_{occ}[a]	1.8	0.7
RR_{em}[b]	6.0	3.9
$RR_{occ/em}$[c]	18.4	35.3
Relative excess risk due to interaction ($RR_{occ/em} - RR_{occ} - RR_{em+1}$)	11.6	31.9

[a] RR_{occ}, relative risk due to occupational exposure in poor and intermediate metabolizers of debrisoquine (*i.e.*, the low risk debrisoquine metabolic phenotype).
[b] RR_{em}, the relative risk in extensive metabolizers of debrisoquine (the high risk metabolic phenotype), in occupationally unexposed individuals.
[c] $RR_{occ/em}$, the relative risk in occupationally exposed individuals who are also extensive metabolizers of debrisoquine.

dividuals with high MRs (PM) are highly likely to be of the homozygous recessive genotype, distinguishing heterozygotes (IM) from homozygous dominant EM on the basis of MR is not entirely reliable even with a mathematically optimized technique for defining the phenotype distributions (14). The pattern of increased risk in EM is not highly dependent on the precise MP definition chosen. This can be demonstrated by comparing Tables 4 and 6 with the corresponding Appendix Tables 1 and 2. The major findings of the study: increased risk of lung cancer in EM, pattern of risk by histology (most in the strongly smoking related histologies, least in adenocarcinomas), and apparent interaction with occupational carcinogen exposure, are quite similar.

For the analysis of occupational associations, we chose to combine the PM and IM groups although on a genetic basis, combining of the homozygous recessive PM with the heterozygous IM may not be entirely appropriate. Our results, however, show no difference between PM and IM in lung cancer risk. Excluding the IM group from the analysis, the comparison between PM and EM shows similar results for occupational lung carcinogens, although the confidence intervals are wider due to the smaller numbers.

This study had some design limitations which may impact on the interpretation of the results. It may be argued that COPD controls are not representative of the general population. A hospital-based control group was considered appropriate for this hospital-based case series since this particular group was readily available, had a similar referral pattern to the cases, and had comparable smoking history. Smoking was considered to be a crucial potential confounder at the time the study was initiated, although subsequent work has not found smoking to influence the debrisoquine MR (14). This and other studies have found the percentage of PM in normal Western populations (range, 5.4–9.4%) to be the same or slightly lower than that of our controls (9.0%, old cutpoints) (15–17).

Data collected for this study included information on current and previous jobs, specific high risk work practices (*i.e.*, inhalation of dust, chemicals, or oils on skin), and occupation in known local locations (*i.e.*, London dockyards) where exposure to carcinogens was likely. A strictly standardized data collection instrument was not used. Certain details of the occupational histories were therefore missing such as the duration and time period of work and industry in which the jobs were held. Some random misclassification of occupational exposure undoubtedly occurred because of the relatively nonspecific information (job title) used to classify subjects. This would be expected especially in the PAH group where the diverse nature and varied carcinogenicity of the class of compounds make job title a less accurate reflection of actual exposures. Based on the available information we identified no subjects with other lung carcinogen exposure (*e.g.*, arsenic, radon). Failure to recognize individuals exposed to other lung carcinogens and the etiological role of some carcinogens in COPD are two sources of bias which would result in an underestimation of the occupational carcinogen lung cancer risks. It would be useful, in further studies, to assess these associations by choosing other control populations and determining whether this association also holds for nonsmokers, and other racial and ethnic groups.

The trend toward increased risk in female debrisoquine EMs noted in each histological subtype could be explained by underreporting of occupational exposure in women (either due to passive exposure from spouses or reduced reporting of occupations in women because of the lack of a standardized instrument). Any unreported occupational (or possibly other carcinogen) exposure could result in an apparent increased risk based on the debrisoquine MP because of the synergistic interaction between these two risk factors. Alternatively, a tumor mediated endocrine (*e.g.*, estrogen) enhancement of debrisoquine metabolism could account for this finding. Further study is required to determine whether a gender difference exists and what its mechanism might be.

Misclassification of the debrisoquine MP due to cancer is another potential source of bias. We know of no evidence that tumor exerts a direct or indirect influence on the genetically determined ability to metabolize debrisoquine. Subjects in this study received no treatment prior to phenotyping so the possible influence of chemotherapy or surgery (anesthesia) is not relevant. It has been reported that other measures of oxidative metabolism (mephenytoin ratio and antipyrine plasma clearance) are unchanged in a small sample of lung cancer patients in whom EM of debrisoquine predominate (18). While all this indirect evidence argues against this type of misclassification, the final resolution of this question will require a prospective study or definitive molecular determination of the genotype.

It is generally accepted that most chemical carcinogens require metabolic activation before initiating the chain of events ultimately leading to neoplasia (19). Although no evidence exists at present that the debrisoquine isozyme participates in the metabolic oxidation of carcinogens in cigarette smoke or of occupational lung carcinogens, a role for the debrisoquine isozyme in carcinogen activation cannot be excluded. The finding of increased risk due to the EM phenotype in the more strongly smoking associated histologies (*i.e.*, small cell and squamous cell), and the failure to demonstrate statistically significant increased risk in adenocarcinomas is indirectly supportive of a role for the debrisoquine metabolizing enzyme in the metabolism of an unspecified carcinogen in tobacco smoke. The debrisoquine isozyme participates in drug metabolism via aliphatic, alicyclic and aromatic hydroxylation, and oxidative *O*-dealkylation (20). The metabolism of at least 20 drugs is influenced by the debrisoquine MP and clinical consequences of this genetically based interindividual variation in metabolic capacity have been described (21–23).

The present study finds that cigarette smokers who are EMs of debrisoquine are at elevated risk of lung cancer. Males who in addition have a history of occupational lung carcinogen exposure are at extremely high risk of lung cancer. The strong nature of the association suggests that if the findings are verified in future studies, debrisoquine phenotyping will provide a useful means of targeting susceptible individuals for lung cancer prevention or screening programs.

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APPENDIX

Appendix Table 1 *Relative risk[a] of lung cancer among debrisoquine EM compared to combined IM/PM by sex and histological sub-type using the traditional metabolic phenotype definitions in individuals with no occupational exposure*

	Males	Females	Total
Cell type	RR (95% CI)	RR (95% CI)	RR (95% CI)
Squamous cell	5.4 (2.0–14.5)	9.5 (3.6–25.2)	7.8 (4.0–15.4)
Small cell	5.6 (1.5–21.6)	12.3 (3.6–41.9)	8.4 (3.5–20.4)
Adenocarcinoma	0.8 (0.2–3.5)	15.4 (1.4–176)	2.5 (0.9–7.2)
All histologies	4.0 (1.9–8.3)	10.5 (4.7–23.5)	6.6 (3.9–11.3)

[a] Adjusted for age, sex, and smoking (pack-years).

Appendix Table 2 *Relative risk[a] for lung cancer in males by occupational lung carcinogen exposure and by the debrisoquine MP using the traditional MP occupational exposure*

	Debrisoquine MP					
	PM/IM			EM		
	Case	CTL	RR (95% CI)	Case	CTL	RR (95% CI)
Asbestos[b]						
None	28	85	1.0	83	36	7.0 (3.9–12.7)
Possible	4	19	0.6 (0.2–1.9)	27	7	11.8 (4.5–30.9)
Likely	4	4	3.0 (0.7–13.2)	13	2	17.2 (3.6–82.6)
PAH[c]						
None	25	65	1.0	51	26	5.3 (2.7–10.4)
Possible	9	38	0.7 (0.3–1.7)	63	19	9.4 (4.6–19.2)
Likely	2	5	0.9 (0.2–5.2)	9	0	

[a] Adjusted for age and smoking (pack-years).
[b] Also adjusted for PAH exposure (unlikely, possible, likely).
[c] Also adjusted for asbestos exposure (unlikely, possible, likely).

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